GENERAL AND DIRECT METHOD FOR PREPARING OLIGONUCLEOTIDE-FUNCTIONALIZED METAL-ORGANIC FRAMEWORK NANOPARTICLES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This is a U.S. National Phase of International Application No. PCT/US2018/042050, filed Jul. 13, 2018, which claims priority to U.S. Provisional Application No. 62/532,241, filed Jul. 13, 2017.

STATEMENT OF GOVERNMENT SUPPORT

[0002] This invention was made with government support under FA9550-14-1-0274 awarded by the Air Force Office of Scientific Research; W911NF-15-1-0151 awarded by the Army Research Office; DMR1121262 awarded by the National Science Foundation; and U54 CA199091 awarded by the National Institutes of Health. The government has certain rights in the invention.

INCORPORATION BY REFERENCE OF MATERIALS SUBMITTED ELECTRONICALLY

[0003] This application contains, as a separate part of the disclosure, a Sequence Listing in computer readable form (Filename: 2017-128_Seqlisting.txt; Size: 4,923 bytes; Created: Jul. 12, 2018), which is incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0004] The present disclosure generally relates to metal-organic framework nanoparticles containing terminal phosphate-modified oligonucleotides, methods for making the same, and methods of using the same.

BACKGROUND

[0005] It is known that DNA is a versatile and powerful ligand for modifying nanomaterials by virtue of its programmable and sequence-specific interactions.[1-3] For example, by densely functionalizing DNA onto spherical nanoparticles (NPs), one can orient the oligonucleotides (3'-5' or 5'-3') and generate spherical nucleic acid-nanoparticle conjugates (SNAs),[4] which exhibit unusual biological properties that have enabled a variety of applications in research and medicine. Indeed, many biodiagnostic systems and therapeutic lead compounds for as gene regulation are now based upon SNAs.[5,6] In addition, they have become the central building blocks for crystal engineering approaches based upon the concept of DNA-programmable assembly.[7-9] Thus far, several approaches have been developed for modifying noble metal,[1,2,10] oxide,[11] quantum dot nanoparticles with DNA.[12] However, there are no general ways for directly modifying MOF nanoparticles with oligonucleotides in a preferential end-on manner. Indeed, all previous approaches have utilized either nonspecific interactions such as electrostatic adsorption and van der Waals interactions, [13,14] or required a coupling agent that is necessarily immobilized on the particle surface prior to functionalization with DNA,[15,16] rendering less control and generality.

SUMMARY

[0006] Herein, a general strategy for functionalizing MOF nanoparticles with oligonucleotides at high density is provided. Using terminal phosphate-modified oligonucleotides, the dense coordinatively unsaturated metal sites (CUS) on a MOF nanoparticle surface can be chemically addressed.[17-21] Solid-state nuclear magnetic resonance (SSNMR) spectroscopy and powder X-ray diffraction (PXRD) confirm that the DNA-functionalization of MOFs occurs by metal-phosphate coordination and that the structural integrity and porosity of the MOF architecture are preserved postmodification (FIG. **1**). As proof-of-concept of generality, this approach was extended to a series of nine different MOFs, featuring four metal nodes (Zr, Fe, Cr, Al) and four different organic linkers.

[0007] Accordingly, in some aspects the disclosure provides an oligonucleotide-functionalized metal-organic framework (MOF) nanoparticle, wherein the oligonucleotide is a terminal phosphate-modified oligonucleotide and the phosphate forms a metal-phosphate bond with the metal ion of the MOF nanoparticle. In some embodiments, the MOF nanoparticle comprises zirconium (Zr), chromium (Cr), iron (Fe), and/or aluminum (Al). In further embodiments, the MOF comprises UiO-66, UiO-67-bpy, UiO68-N_3/PCN-58, PCN-222/MOF-545, PCN-223, PCN-224, MIL-101 (Al), MIL-101 (Fe), or MIL-101(Cr).

[0008] In some embodiments, the terminal phosphate-modified oligonucleotide has a phosphate group on its 3' end. In further embodiments, the terminal phosphate-modified oligonucleotide has a phosphate group on its 5' end. In some embodiments, a nanoparticle of the disclosure further comprises an agent selected from the group consisting of a peptide, a protein, a nanoparticle, an antibody, a small molecule, and a combination thereof, wherein the agent is encapsulated in the nanoparticle.

[0009] In some embodiments, the terminal phosphate-modified oligonucleotide comprises a $(GGT)_n$ nucleotide sequence, wherein n is 2-20. In further embodiments, density of terminal phosphate-modified oligonucleotide on the surface of the MOF nanoparticle is from about 2 pmol/cm^2 to about 24 pmol/cm^2. In some embodiments, the MOF nanoparticle comprises a plurality of terminal phosphate-modified oligonucleotides on its surface and at least one oligonucleotide regulates gene expression. In some embodiments, the at least one terminal phosphate-modified oligonucleotide is an antisense oligonucleotide. In further embodiments, the terminal phosphate-modified oligonucleotide is RNA. In still further embodiments, the RNA is small interfering RNA (siRNA).

[0010] In some aspects, the disclosure provides a method of making an oligonucleotide-functionalized MOF nanoparticle of the disclosure, comprising (a) mixing a metal ion and a multi-dentate ligand to form the MOF nanoparticle; and (b) contacting the MOF nanoparticle with a plurality of the terminal phosphate-modified oligonucleotides, thereby producing the oligonucleotide-functionalized MOF nanoparticle, such that the phosphate groups of the terminal phosphate-modified oligonucleotides associate with coordinatively unsaturated metal sites (CUS) on the MOF nanoparticle surface via a metal-phosphate bond. In some embodiments, the multi-dentate ligand comprises 2, 3, or 4 coordinating functional groups. In further embodiments, the multi-dentate ligand is a bi-dentate ligand. In still further embodiments, the multi-dentate ligand is a tri-dentate